DETAILED ACTION

1. Claims 1-18 are all the pending claims for this application.

2. Claims 1, 2, 3, 6, 7 and 13 were amended in the Response of 4/2/08.

3. Claims 8-12 and 16-18 are withdrawn from examination.

4. Claims 1-7 and 13-15 are all the pending claims under examination.

5. Applicants amendments to the claims have necessitated new grounds for rejection. This action is FINAL.

Information Disclosure Statement

6. The IDS filed 9/15/05 did not include copies of the references on the 1449 form and the references did not enter the U.S. national stage with the 371 application. Therefore, the references are stricken on the attached copy of the 1449 form.

7. The second request for an initialed copy of the 1449 from the IDS 9/15/05 is acknowledged, but copies of the missing references were not provided with the filing on 10/29/07 or upon national stage entry of this application.

8. The IDS of 1/22/08 has been considered and entered and the copy of the examiner's initialed 1449 form is attached. These references are considered to be the same as the missing references cited on the 1449 form from the IDS of 9/15/05 and those referred to in the second request for consideration of 10/29/07.

9. The IDS of 5/22/08 has been considered and entered and the copy of the examiner's initialed 1449 form is attached.

Withdrawal of Objections

Drawings

10. The Replacement Sheets containing the corrected drawing figure(s) for Figures 1 and 2 along with the marked-up copy of each Replacement Sheet including annotations indicating the changes made to the previous version has been entered.

Withdrawal of Rejections

Claim Rejections - 35 USC § 102

11. The rejection of Claims 1, 2, 4-7, 14 and 15 under 35 U.S.C. 102(e) as being anticipated by Winter et al. (US2004/0219643; published 11/4/04; priority filing date 6/28/02; cited in the 892 form of 12/7/06) is withdrawn.

Applicants' allegations on pp. 10-16 of the Response of 4/2/08 have been considered and are found persuasive, more especially in view of the newly amended generic claims. Applicants allege Winter does not disclose host cells secreting an antibody heavy chain and Winter did not take a light chain expressing phage library and introduce the library into the host cells or take a first antigen-selected phage library and introduce that into host cells secreting a second antibody heavy chain. Further Winter's purpose was different because the VL and VH are both directed against different ligands whereas in the instant case the light chain is selected for its ability to act as a "common" light chain able to associate with different heavy chains to facilitate antigen binding of the heavy chains to the cognate ligands.

Claims - 35 USC § 103

12. The rejection of Claims 1-3 and 13 under 35 U.S.C. 103(a) as being unpatentable over Winter as applied to claims 1 and 2 above, and further in view of Goldstein et al. (J. Immunol. 158:872-879 (1997); cited in the PTO 892 form of 2/16/07) is withdrawn.

Applicants' allegations on pp. 16-18 of the Response of 4/2/08 have been considered and are found persuasive, more especially in view of the newly amended generic claims. Applicants allege that Winter is not an effective primary reference because the methods are neither disclosed or obvious over Winter and where Goldstein does not rectify this deficiency.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

13. Claims 1-7 and 13-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

Nature of the Invention/ Skill in the Art

Claims 1 and 3-6 are interpreted as being drawn to a method of screening for commonly shared antibody light chains which correspond to two or more types of different antibody heavy chains where in the initial step host cells "secreting" the heavy chain against a target antigen are provided, then a phage library encoding a plurality of different light chains is introduced into the host cells in order to secrete a library of phage particles presenting the heavy chain and a light chain, where the library is screened for specific binding to the target antigen, then where the screened library is introduced into host cells "secreting" a second heavy chain that binds to a different antigen than the first antigen in order to secrete a library of phage particles presenting the second heavy chain and a light chain, and finally where the phage libraries produced from the second introducing step are selected for binding to the second target antigen (Claim 1), where the first and second heavy chains are Fd (Claim 3), the host is E. coli (Claim 4), the steps are performed twice or more (Claim 5) and the method further comprises introducing the second screened phage particle library into a host

"secreting" a third heavy chain that binds to a third and different antigen from the first and second antigens and selecting the phage particle library that bind to the third antigen (Claim 6).

Claims 2, 7 and 13-15 are interpreted as being drawn to a method of screening for commonly shared antibody light chains which correspond to two or more antibody heavy chains of different amino acid sequence where in the initial step host cells "secreting" the heavy chain against a target antigen are provided, then a phage library encoding a plurality of different light chains is introduced into the host cells in order to secrete a library of phage particles presenting the heavy chain and a light chain, where the library is screened for specific binding to the target antigen, then where the screened library is introduced into host cells "secreting" a second heavy chain comprising a different amino acid sequence than the first heavy chain in order to secrete a library of phage particles presenting the second heavy chain and a light chain, and finally where the phage libraries produced from the second introducing step are selected for binding to the target antigen recognized by the second antibody (Claim 2), and the method further comprises introducing the second screened phage particle library into a host "secreting" a third heavy chain having an amino acid sequence different from the first and second heavy chain and selecting the phage particle library that bind to the antigen recognized by the third heavy chain (Claim 7), where the first and second heavy chains are Fd (Claim 13), the host is E. coli (Claim 14), and the steps are performed twice or more (Claim 15).

The relative skill in the art required to practice the invention is a molecular immunologist with a background in phage display library production and screening for recombinant antibodies.

Disclosure in the Specification

The specification generally teaches methods of screening for commonly shared light chains which correspond to two or more types of different antibody heavy chains. Hosts which secrete heavy chains of antibodies that bind to desired antigens must be obtained first. Two types of hosts that each secretes a heavy chain corresponding to one of the two types of desired antigens are necessary for generating a BsAb, three types are necessary for a tri-specific antibody, and four types are necessary for a tetra-specific antibody. To obtain these hosts, the specification teaches producing antibody-producing cells from mammals (p. 7, lines 9-28). Host cells that secrete antibody heavy chains may secrete full-length antibody heavy chains or partial fragments (p. 10, lines 21-23). A gene portion that encodes a desired antibody heavy chain is introduced into an expression vector that is suitable for expression in appropriate host cells. Host cells are preferably bacteria that can be infected by phages, particularly gram negative bacteria (p. 10, lines 30-35). Phage particles contemplated by the invention are listed on p. 12, lines 20-23.

The following examples are provided for performing method steps:

Eukaryotic host cell/ expression vector (working example): the specification at p. 13, lines 2-16 incorporates by reference the disclosure from WO 95/15393 for constructing antibody libraries using eukaryotic cells that present antibodies on their cell

surfaces. An expression vector carrying a gene that encodes a desired heavy chain (for example, Fd), and is linked downstream of a promoter appropriate for its expression and a signal sequence which enables the secretion of the heavy chain, is introduced into eukaryotic host cells. Expression vectors are constructed with light chain-encoding genes linked to a transmembrane region-encoding sequence and inserted downstream of an appropriate promoter, so that the light chains will be displayed on cell surfaces when expressed. By introducing light chain expression vectors into the aforementioned heavy chain-secreting host cells, host cells which *express on their cell surfaces* antibodies that bind to a desired antigen can be selected. The displayed antibody is a Fab fragment when Fd is used as the heavy chain and those comprising VL and CL are used as the light chains.

Bacterial host cell/ phage library (prophetic example): A light chain library is introduced into the E. coli host which expresses an antibody A heavy chain (for example, Fd), and by infecting the host with helper phages, a phage library, which presents *on their surfaces* antibodies comprising an antibody A heavy chain and various light chains (Fab when the heavy chain is Fd and the light chain comprises VL and CL) as fusion proteins (p. 12, line 30- p. 13, line 1).

The specification is enabling for using a host cell system compatible with a phage library being introduced into the host cell such as a bacterium which produces phage particles expressing an assembled antibody heavy and light chain on the particle surface after following the method steps. The specification is not enabling for introducing a phage library into just any host cell much less where the host cell is a

eukaryotic cell. The specification is not enabling for any host cell having the ability to "secrete" an antibody heavy chain much less where a bacterial host cell secretes the first or second or third antibody heavy chain. The claims encompass any host cell a) having the ability to secrete an antibody heavy chain and b) capable of being infected with a phage particle library whereas the specification is only enabling for using phage particles to infect a bacterium where at most the resultant, selected phage particle library also expresses the heavy chain and light on the surface. The specification is not enabling for the genus of host cells having all of the properties of the instant claimed method.

Prior Art Status: E. coli host cells express and transport antibody fragments comprising a bacterial signal peptide into the periplasmic space

The prior art does not recognize bacterial cells, more specifically E. coli, as being capable of secreting antibody fragments absent the fragment being engineered to have a bacterial signal peptide. As reviewed by Kipriyanov et al. (Molec. Biol. 12: pp. 173-201 (1999)) E. coli can express antibody fragments such as Fab, Fv and scFv into the periplasm. "Periplasmic expression has permitted the functional testing of a wide variety of antibody fragments with different antigen binding specificities. The antibody fragments are usually correctly processed in the periplasm, they contain intramolecular disulfide bonds and are soluble. However, the high-level expression of a recombinant protein with a bacterial signal sequence in E.coli often results in the accumulation of insoluble antibody fragments after transport to the periplasm, presumably via the aggregation of a folding intermediate"...and "high protein concentrations of the secreted

antibody fragment in the periplasmic space would favor the formation of insoluble aggregates over correct folding."

Thus one of skill in the art could not even predict that any antibody heavy chain could be "secreted" by any host cell much less a bacterium and that the same host cell could be infected with a library of phage particles encoding any random antibody light chain where the host cell then produced a phage particle expressing on its cell surface an assembled heavy and light chain antibody with specific antigen binding ability or at least antigen binding ability for the recognized antigen of the heavy chain. Because of the lack of working examples in the specification for the scope of host cells encompassed by the instant method claims, the ordinary artisan would be forced into undue trial and error experimentation to practice using the method based on the written description in the specification alone.

Conclusion

14. No claims are allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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